

Proposition 65 Proposed Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Acrylamide

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Office of Environmental Health Hazard Assessment (OEHHA) Reproductive and Cancer Hazard Assessment Branch

SUMMARY

The proposed maximum allowable dose level (MADL) for acrylamide is **140 micrograms/day ($\mu\text{g}/\text{day}$)**. This value is based on the male reproductive effects of acrylamide as observed in the drinking water study in male rats by Tyl et al. (2000). The MADL is calculated based on a human male body weight of 70 kg (Title 27, California Code of Regulations, section 25803(b))¹.

BACKGROUND

This report describes the derivation of a maximum allowable dose level (MADL) for acrylamide (CAS No. 79-06-1).

Acrylamide is used in the formation of plastics and grouting agents. However, the general public is exposed to acrylamide primarily through certain foods that have been cooked at high-temperature, and through cigarette smoke. Plant based foods that are rich in carbohydrates and low in protein can form acrylamide when they are cooked at high temperature.

Acrylamide has been proposed for listing under Proposition 65² as known to the State to cause reproductive toxicity (developmental and male reproductive toxicity). The proposed listing is based on formal identification of acrylamide as causing developmental and male reproductive toxicity by the National Toxicology Program (NTP) in its final report titled "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide" (NTP-CERHR, 2005). The NTP, solely as to final reports of the NTP's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR), is a body recognized as authoritative for the listing of chemicals as known to cause reproductive toxicity under Proposition 65 (Section 25306(1)).

OEHHA will adopt a final MADL for acrylamide into regulation only if acrylamide is

¹ All further references to regulations are to Title 27 of the California Code of Regulations, unless otherwise noted

² The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code, section 25249.5 et seq.

added to the Proposition 65 list as known to the state to cause reproductive toxicity. Procedures for the development of Proposition 65 MADLs are provided in Sections 25801 and 25803. Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulation, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality. The NOEL shall be the highest dose level which results in no observable reproductive effect expressed in milligrams of chemical per kilogram of bodyweight per day.

STUDY SELECTION

The NTP-CERHR Monograph (NTP-CERHR, 2005) identified the most sensitive studies considered to be of sufficient quality for identifying acrylamide as causing developmental and male reproductive toxicity. OEHHA considers those studies to be of sufficient quality for use in determining a MADL. Relevant studies or reports that provide information on the developmental or male reproductive toxicity of acrylamide that were published after the NTP-CERHR review was completed have been identified through literature searches. OEHHA also reviewed these later studies as the possible basis for the MADL.

Section 25803 states that “where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL.”

Human Studies

No human data relevant for establishing a MADL based on the reproductive or developmental effects of acrylamide were identified by NTP-CERHR (NTP-CERHR, 2005) or in the subsequent literature search by OEHHA.

Studies in Laboratory Animals

The LOELs and NOELs from studies of sufficient quality that may provide the basis for the establishment of the MADL are discussed below. For full description of the studies the reader is referred to the NTP-CERHR Monograph or the original citation.

Developmental Toxicity

The “NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide” (NTP-CERHR, 2005) identifies a Lowest Observed Adverse Effect Level (LOAEL) of 4-5 milligrams per kilogram body weight per day (mg/kg bw/day) for developmental toxicity in rats exposed to acrylamide in drinking water. This is based on marginally decreased pup weight

postnatally and at weaning in a reproductive toxicity study by Zenick et al. (1986). The NTP-CERHR report noted that “it could not be determined if developmental toxicity was due to maternal gestational or lactational treatment, or both.” Due to this uncertainty, this study has limitations as the basis for a MADL.

A LOAEL of 45 mg/kg bw/day and a No Observed Adverse Effect Level (NOAEL) of 15 mg/kg bw/day were identified in mice exposed via gavage in a study by Field et al. (1990) on the basis of decreased fetal weight per litter.

Two studies indicative of developmental toxicity published after the NTP-CERHR monograph were identified by OEHHA (Hill et al., 2008; Takahashi et al., 2008). The study by Takahashi et al. (2008) identified a LOEL of 9.9 mg/kg bw/day, the lowest dose tested. The study by Hill et al. (2008) was an in vitro study of developmental neurotoxicity, and so did not provide an appropriate NOEL or LOEL for in vivo exposure.

Male Reproductive Toxicity

The NTP-CERHR Monograph (NTP-CERHR, 2005) identifies a LOAEL of 5 mg/kg bw/day for male reproductive toxicity in rats in the dominant lethal component of this drinking water study based on decreased litter size and/or increased post-implantation loss, indicative of genetic effect in sperm (Tyl et al., 2000). A NOAEL of 2 mg/kg bw/day acrylamide was identified (Tyl et al., 2000).

Seven studies indicative of male reproductive toxicity published after the NTP-CERHR monograph were identified by OEHHA. Several studies examined effects on testicular DNA or gene expression (Dobrzyska, 2007; Marchetti et al, 2009; Yang et al., 2005b), or testicular apoptosis (Chen et al, 2006). One study was of dominant lethality (Ghanayem et al., 2005) and two studies examined testicular, epididymal and sperm parameters (Wang et al., 2007; Yang et al., 2005a;). Two studies (Yang et al., 2005a; Yang et al., 2005b) identified LOELs of 5 mg/kg bw/day, the lowest dose tested, consistent with the LOAEL identified by NTP-CERHR (NTP-CERHR, 2005). One study identified a NOEL of 5 mg/kg bw/day and a LOEL of 10 mg/kg bw/day (Wang et al., 2007). The remaining studies identified NOELs and/or LOELs greater than 10 mg/kg bw/day.

Study Basis for the MADL calculation

The study by Tyl et al. (2000) provides a NOEL of 2 mg/kg bw/day for male reproductive toxicity that is lower than the lowest empirical NOEL identified for developmental toxicity, 15 mg/kg bw/day in the study by Field et al. (1990). The NOEL of 2 mg/kg bw/day for male reproductive toxicity is the highest NOEL that does not exceed the lowest LOEL of 5 mg/kg bw/day, and so is the appropriate basis for calculation of the MADL.

Briefly, Tyl et al. conducted a 2-generation reproduction study with exposure to 0.5, 2.0 or 5.0 mg/kg bw/day acrylamide via drinking water (with concentrations in water adjusted weekly to maintain these doses). Some males in the F0 generation were continued on into a dominant lethal study, with significant reductions in live pups/litter in the F0 and F1 generations and a significant increase in post-implantation loss in the F0 generation at 5.0 mg/kg bw/day.

MADL CALCULATION

The NOEL is the highest dose level that results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day. The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 25803(b)). When the applicable reproductive effect is upon the male, the MADL is calculated based on a human body weight of 70 kg.

The following calculations were performed to derive the MADL for acrylamide via the oral route of exposure, based on a NOEL of 2 mg/kg-day for male reproductive effects observed in rats by Tyl et al. (2000).

Calculation of the NOEL for a 70 kg man:

$$2 \text{ mg/kg-day} \times 70 \text{ kg} = 140 \text{ mg/day}$$

The proposed MADL is derived by dividing the NOEL by one thousand (Section 25801(b)(1)). Thus, the NOEL was divided by 1,000 to obtain the MADL.

$$\text{Proposed MADL} = 140 \text{ mg/day} \div 1000 = \mathbf{140 \text{ }\mu\text{g/day}}$$

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